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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/827,255	04/05/01	WONG J	144183000133

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HM22/1106

EXAMINER	
SCHMIDT,M	
ART UNIT	**PAPER NUMBER**
1635	4

DATE MAILED: 11/06/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/827,255	WONG ET AL.	
	Examiner	Art Unit	
	Mary Schmidt	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-8 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-8 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 3, 4, 6 and 8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 3 is indefinite since it is unclear how a cDNA "encodes" a ribozyme or an antisense DNA.

Claim 4 is indefinite since it is an improper Markush claim.

Claim 6 contains a typographical error: "linkaes" should read "linkages.

Claim 8 is indefinite for failing to specify a final step of the method which relates back to the preamble. Specifically, the method steps do not teach that the liver cancer proliferation in inhibited upon administration of the specified compositions.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 1-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Allen et al., Perez-Solar et al., Pratt et al, Martin, Hortobagyi, Menezes et al Neitchev et al. and Mayer et al.

Allen et al. is relied upon to teach targeted liposomal drug delivery: "One way to increase the therapeutic index of drugs such as anticancer drugs, which have low therapeutic indices would be by specifically targeting the drugs to the diseased cells." (See abstract) They specifically teach Ab-biotin coupling mechanisms on page 120, for example. They teach that any ligands may be coupled to such liposomes. They do not specifically teach desialyated glycoprotein-alpha-1. They do teach doxorubicin loaded liposomes on page 127.

Hortobagyi is further relied upon to teach anthracyclines as drugs used in treatments of cancer. They teach liposomal encapsulation of doxorubicin but do not teach coupling to desialyated glycoprotein-alpha-1.

Martin is further relied upon to teach liposomal doxorubicin administration compositions for the treatment of cancer but do not teach coupling to desialyated glycoprotein-alpha-1.

Menezes et al. is relied upon to teach Bcl-2 antisense/dox liposomal compositions but do not teach coupling to desialyated glycoprotein-alpha-1.

Pratt et al. and Mayer et al. are both relied upon to teach the advantage of "liposomal anthracycline formulations is the potential for reductions in observed dose-limiting cardiotoxicity relative to either daunorubicin or doxorubicin as free drug" (Pratt et al. Page 47) and that

"doxorubicin could be administered at >2-fold higher doses when entrapped in liposomes" (Mayer et al, page 105, lines 6-7).

Perez-Soler et al. is relied upon to teach "the potential advantages of liposome-encapsulated doxorubicin are a reduced cardiotoxicity as a result of lower cardiac drug levels and an increased activity against tumors that infiltrate the liver and spleen. Different investigators showed a few years ago that liposome entrapment of doxorubicin results in a reduction of drug-related cardiotoxicity in animals." (P. 4260)

Park et al. is relied upon to teach that "the ASGPR (asialoglycoprotein receptor) system is also considered as a novel approach for targeted gene or drug delivery into liver cells." (P. 304) They are thus relied upon to teach the motivation of using agents which bind the asialoglycoprotein receptor, which encompasses glycoprotein agents, for targeted drug delivery to the liver.

Neitchev et al. is relied upon to teach liposomes having alpha-1 glycoprotein. They do not specifically teach use of such liposomes to targeted delivery of therapeutic compositions to the liver, although liposomes are generally regarded in the art for use in delivery of pharmaceutic compositions and glycoproteins associate with the ASGPR receptor.

It would have been prima facie obvious at the time the invention was made for one of ordinary skill in the art to make a composition for targeted delivery of a therapeutic agent to a tissue, such as liver tissue, expressing asialoglycoprotein receptors comprising an agent such as a cytotoxic drug such as antracyclines (doxorubicin, vincristine, daunorubicin, etc.) or an antisense

(such as the antisense taught by Menezes et al.) encapsulated in a liposome coupled to a targeting agent to the asialoglycoprotein receptors such as the alpha1-acid glycoprotein taught by Neitchev et al. since formation of anthracycline-liposome formulations was well-known in the art for the treatment of cancers and more specifically, targeting asialoglycoprotein receptors was well-known in the art for targeting liver cells. It would have further obvious to couple the glycoprotein-alpha1 by well-known means to the liposome as taught by Allen et al. It would have been further obvious to use such formulations for methods of targeting the compositions to cancerous liver tissues for the benefits taught by Pratt et al., Mayer et al., and Perez-Soler et al.

One of ordinary skill in the art at the time the invention was made would have been motivated to make anthracycline containing liposomes for treatments of various cancers as taught by Hortobagyi and Martin for instance and having any type of targeting agent coupled to the liposome (Allen et al.). One of ordinary skill in the art would have been motivated to administer such compositions for the benefits taught by Mayer et al., Pratt et al, and Perez-Soler et al. Park et al. further taught the specific motivation for use of asialoglycoprotein receptors for drug delivery to liver cells and liposomes specifically containing alpha-acid glycoprotein as taught by Neitchev et al.

One of ordinary skill in the art would have had an expectation of success to design compositions for the targeted delivery of a known therapeutic agent to a tissue, such as liver tissue, expressing asialoglycoprotein receptors since (1) anthracycline/liposome compositions were well-known in the art as taught above, (2) Perez-Soler et al. taught the accumulation of such

compositions in liver cells in the absence of specific targeting, (3) compositions such as alpha-1-acid glycoprotein were known in the art as coupled to liposomes and specific drug targeting to asialogycoprotein receptors was also known in the art, as were (4) many coupling mechanisms known in the art for specific conjugation of targeting agents to liposomes (Allen et al.). Although one of ordinary skill in the art would not have had an expectation of success for any possible therapeutic agent to be delivery for treatment effects of any disease in whole organisms, one of skill in the art would have had the expectation that known anthracycline/liposomes coupled to glycoprotein alpha-1 would have had an expectation for having some success in targeting the liver cells for therapeutic purposes.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to *Mary M. Schmidt*, whose telephone number is (703) 308-4471.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *John LeGuyader*, may be reached at (703) 308-0447.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group Analyst, *Katrina Turner*, whose telephone number is (703) 305-3413.

SEAN McGARRY
PRIMARY EXAMINER

M. M. Schmidt
November 4, 2001

Attachment for PTO-948 (Rev. 03/01, or earlier)
6/18/01

The below text replaces the pre-printed text under the heading, "Information on How to Effect Drawing Changes," on the back of the PTO-948 (Rev. 03/01, or earlier) form.

INFORMATION ON HOW TO EFFECT DRAWING CHANGES

1. Correction of Informalities -- 37 CFR 1.85

New corrected drawings must be filed with the changes incorporated therein. Identifying indicia, if provided, should include the title of the invention, inventor's name, and application number, or docket number (if any) if an application number has not been assigned to the application. If this information is provided, it must be placed on the front of each sheet and centered within the top margin. If corrected drawings are required in a Notice of Allowability (PTOL-37), the new drawings **MUST** be filed within the **THREE MONTH** shortened statutory period set for reply in the Notice of Allowability. Extensions of time may NOT be obtained under the provisions of 37 CFR 1.136(a) or (b) for filing the corrected drawings after the mailing of a Notice of Allowability. The drawings should be filed as a separate paper with a transmittal letter addressed to the Official Draftsperson.

2. Corrections other than Informalities Noted by Draftsperson on form PTO-948.

All changes to the drawings, other than informalities noted by the Draftsperson, **MUST** be made in the same manner as above except that, normally, a highlighted (preferably red ink) sketch of the changes to be incorporated into the new drawings **MUST** be approved by the examiner before the application will be allowed. No changes will be permitted to be made, other than correction of informalities, unless the examiner has approved the proposed changes.

Timing of Corrections

Applicant is required to submit the drawing corrections within the time period set in the attached Office communication. See 37 CFR 1.85(a).

Failure to take corrective action within the set period will result in **ABANDONMENT** of the application.